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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,738	11/30/2001	Philip Gotwals	A076 US	4464

7590 10/21/2003

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/996,738	GOTWALS ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/25/03 has been entered.

2. Claims 1-7 are pending and currently under consideration.

3. The specification is objected to under 37 CFR 1.821(d) for failing to provide a sequence identifier for each individual sequence. Page 30, lines 23-26 has described the four nucleic acid sequence that must have a sequence identifier. Correction is required.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrases "equivalent thereof, or naturally occurring variants thereto" and " a dosage of between about 10mg to about 250 mg administered over a dosing period of between about one to about seven days" claimed in claim 1, lines 5-9 represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 8-25-03 does not point to the specification for support for the newly added limitations "equivalent thereof, or naturally occurring variants thereto" and " a dosage of between about 10mg to about 250 mg administered over a dosing period of between about one to about seven days" as claimed in claim 1. However, the specification does not provide a clear support of those limitations. It is noted that the specification on page 19, lines 1-13, discloses dosage ranges of 0.001 and about 100 mg/kg, 0.1-50 mg/kg and 0.1-20mg/kg of body weight at intervals of every 1-14 days. The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,788,966 (IDS Ref. No. AA) as is evidenced by the specification disclosed on page 36, lines 7-8.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

The `966 patent teaches a method for treating arthritis (see the entire document and column 10, reference claims 1-8 and column 8 lines 65-67 in particular) that is associated with elevated levels of VLA-1 comprising administering to a human a monoclonal antibody 1B3.1 or a fragment thereto (column 3 lines 5-10) that inhibits collagen binding to VLA-1 (see entire document and reference claims 1-8, column 10 in particular). Furthermore, the `966 reference teaches that IB3.1 antibody recognizes an epitope on VLA-1 protein (see column 8 lines 39-46 in particular). The `966 patent further teaches that the increased prevalence of last state T cell activation antigen or VLA-1 in active juvenile chronic arthritis (column 1 line lines 56-57 in particular).

The claimed invention differs from the reference teachings only by the recitation of a function blocking antibody or fragment of said antibody, capable of binding an epitope of VLA-1, wherein the epitope consists of the amino acids of SEQ ID NO:8, or equivalents thereof, or naturally occurring variants thereof and a dosage of between about 10 mg to about 250 mg administered over a dosing period of between about one to about seven days in claim 1.

While the prior art teachings may be silent as to the "wherein the epitope consists of the amino acids Val-Gln-Arg-Gly-Gly-ARG (SEQ ID NO:8" per se; The `966 patent teaches that the product, 1B3.1 monoclonal antibody reacts with long term activated T cell lines but not with resting or short-term activated T cells. Further, the target antigen of MoAb 1B3.1 consists of proteins of 200 and 110 kDa that are identical to VLA-1 proteins (see col. 8, lines 38-45 in particular), which is the same as the claimed product (functional antibody). As is evidenced by the specification on page 36, lines 7-8, that all the function-blocking mAbs recognizes the chimeric I domain.

The `966 patent does not explicitly teach the dosage of between about 10 mg to about 250 mg administered over a dosing period of between about one to about seven days.

It is clear that both the prior art and claimed method administer the same treatment to achieve the same results. It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II.

The recitation of "decrease in arthritis score of about 65%, 79%, 85%, 90% or greater" of claims 1-4 is considered inherent properties of the reference antibody because the antibody 1B3.1 used in the reference method is the same as the antibody used in claimed method.

From the combined teaching of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 8/25/03, have been fully considered, but have not been found convincing

Applicant argues that even if the 1B3.1 monoclonal antibody does target the same epitope-which it may-the Applicants' claimed methods of treatment are not expressly or inherently anticipated by the `966 patent because there are manipulative differences between the steps of each of the pending claims and the disclosure of the `966 patent. Applicant argues that the `966 patent dose not disclose, either expressly or inherently, administration of an antibody or antibody fragment in a dosage of between about 10 mg to about 250 mg administered over a dosing period of between about one to about seven days to provide a decrease in arthritic score of about 65% or greater when compared to a control antibody treated subject.

However, the determination of the optimal dosage and the duration of treatment is well within the purview of one of ordinary skill in the art at the time the invention was made and lends no patentable import to the claimed invention. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II.

8. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,788,966 (IDS Ref. No. AA) in view of Riikonen *et al* (Biochemical and Biophysical Research Communication 209:205-212, 1995) and Fabbri *et al* (IDS Ref. No. CB).

The teachings of `966 patent have been discussed, supra. The `966 further teaches that members of a protein complex called very late antigens (VLA) are expressed on the surface of T-cells (column 1 lines 23-25 in particular). Finally, the `966 patent teaches that VLA-1 molecule is involved in the binding of extracellular matrix materials (ECM) (column 8 lines 52-54 in particular).

The claimed invention differs from the reference teachings only by the recitation of a function blocking antibody or fragment of said antibody, capable of binding an epitope of VLA-1, wherein the epitope consists of the amino acids of SEQ ID NO: 8 in claim 1.

Riikonen *et al* teaches that $\alpha 1\beta 1$ integrin is also known as very late activation antigen-1 (VLA-1) and in vivo $\alpha 1\beta 1$ integrin expression is seen in synovial lymphocytes of patients with rheumatoid arthritis (page 205 last paragraph in particular).

Fabbri *et al* teaches a functional monoclonal antibody (FB12) recognizing the human $\alpha 1$ integrin I-domain. Fabbri *et al* further teaches that FB12 mAB efficiently and specifically inhibits the binding of activated human lymphocytes to laminin, collagen type IV and fibronectin (see the entire document and page 48, left column 2nd paragraph in particular). Finally, Fabbri *et al* teaches that the $\alpha 1$ I domain has functional role in lymphocyte binding to ECM protein.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the 1B3.1 monoclonal antibody taught by the `966 patent with functional monoclonal antibody FB12 as taught by Fabbri *et al* in a method of treating rheumatoid arthritis.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because FB12 monoclonal antibody has a functional role in lymphocyte binding to ECM protein as taught by Fabbri *et al* a critical molecule in synovial lymphocytes of patients with rheumatoid arthritis as taught by Riikonen *et al*.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant argues that Fabbri concluded that the FB12 mAb: "may represent a useful reagent for the study of the biological function of $\alpha 1$-1 integrin I domain" and that the results "suggest that the $\alpha 1$-1 domain has a functional role in lymphocyte binding to ECM proteins, including FN". Applicant contended that this was not a clear motivation to combine the cited references to yield

the specific methods of treatment recited in the pending and new claims. Applicant concluded that the FB12 mAb could serve as research tool to learn more about the α1-1 domain.

However, the fact remain that the FB12 mAb is a functional blocking antibody that recognize the human α1 integrin I-domain, as the claimed antibody. While Fabbri et al does not expressly teach SEQ ID NO:8, however binding to SEQ ID NO: 8 is an expected property of FB12 mAb. The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07.

9. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,788,966 (IDS Ref. No. AA) in view of Riikonen *et al* (Biochemical and Biophysical Research Communication 209:205-212, 1995).

The teachings of `966 patent have been discussed, supra. The `966 further teaches that members of a protein complex called very late antigens (VLA) are expressed on the surface of T-cells (column 1 lines 23-25 in particular). Finally, the `966 patent teaches that VLA-1 molecule is involved in the binding of extracellular matrix materials (ECM) (column 8 lines 52-54 in particular).

The claimed invention differs from the reference teachings only by the recitation of a function blocking antibody or fragment of said antibody, capable of binding an epitope of VLA-1, wherein the epitope consists of the amino acids of SEQ ID NO: 8 in claim 1.

Riikonen *et al* teaches a functional monoclonal antibody (SR-84) recognizing the human α1 subunit which inhibit the adhesion of cells to matrix molecules. Riikonen *et al* further teaches that SR-84 mAB completely block the adhesion of Hela cells to type IV collagen (see the entire document and page 207 last paragraph in particular). Furthermore, Riikonen *et al* teaches that α1β1 integrin is also known as very late activation antigen-1 (VLA-1) and in vivo α1β1 integrin expression is seen in synovial lymphocytes of patients with rheumatoid arthritis (page 205 last paragraph in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the 1B3.1 monoclonal antibody taught by the `966 patent with functional monoclonal antibody SR-84 as taught by Riikonen *et al* in a method of treating rheumatoid arthritis.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because SR-84 monoclonal antibody inhibits the adhesion of VLA-1 with different collagenous components of extracellular matrix (ECM), and hence its important in α1β1 integrin seen in synovial lymphocytes of patients with rheumatoid arthritis as taught by Riikonen *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant argues that the`966 and Riikonen et al, do not suggest the therapeutic endpoint and dosage regimen recited as limitations of the pending amended claims and do not render any of the claims obvious. Applicant continues to argue that such particular dosage regimens would achieve the defined therapeutic endpoint.

Again, the determination of the optimal dosage and the duration of treatment is well within the purview of one of ordinary skill in the art at the time the invention was made and lends no patentable import to the claimed invention. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
October 20, 2003

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